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Management for Patients With Advanced T4 Epidermoid Carcinoma of the Esophagus

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Available data concerning the treatment of patients with advanced T4 esophageal carcinoma are limited. A consecutive series of 42 patients with advanced T4M0 epidermoid carcinoma of the esophagus were studied from June 1987 to July 1992. The aim of this study was to evaluate the efficacy of various therapeutic modalities, and further evaluate the therapeutic options. The various therapeutic modalities included the following: Group I, feeding jejunostomy or endoesophageal intubation, 6 patients; Group II, palliative subtotal esophagectomy only, 8 patients; Group III, bypass procedures without tumor resection, 9 patients; Group IV, nutritional support and then treatment with irradiation (n = 8) or concurrent radio-chemotherapy (n = 4), 12 patients; Group V, subtotal esophagectomy, followed by aggressive concurrent radiochemotherapy, 7 patients. The total prescribed irradiation dose was 60 Gy (10 Gy/5 fractions/week). A combination regimen of chemotherapy consisted of cisplatin, 5-fluorouracil, and leucovorin (PFL regimen).

For the patients undergoing esophagectomy or bypass procedures (n = 24), the rates of operative complication and mortality were 45.8% and 25%, respectively. Side effects of adjuvant therapy (n = 24) consisted of main airway irritation (100%), mucositis or gastrointestinal symptoms (83.3%), hematologic toxicity (79.2%), esophagitis or gastric ulcer (62.5%), alopecia (37.5%), and pneumonia (20.8%). The mortality due to toxicity of adjuvant therapy was 21.1% (4/19 patients). The mean survival times for each of the different groups was 1.9 ± 0.5 months for Group I, 4.8 ± 1.6 months for Group II, 5.2 ± 1.2 months for Group III, 7.3 ± 2.0 months for Group IV, and 20.3 ± 2.5 months for Group V, respectively. Compared with patients of Groups I–IV, the Group V patients had a significantly superior one-year survival rate ($P < 0.01$).

Our results demonstrated that esophagectomy followed by concurrent irradiation and PFL combination chemotherapy may provide a significant improvement in the quality of life and survival for appropriate patients with advanced T4M0 epidermoid carcinoma of the esophagus. Furthermore, more than one cycle of PFL regimen chemotherapy may result in

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a better prognosis. During the performance of such an aggressive treatment, the utmost care must be taken with the patient's nutrition and to prevent pulmonary complications.

KEY WORDS: esophageal carcinoma, esophagectomy, radiochemotherapy

INTRODUCTION

Carcinoma of the esophagus is a rather common disease amongst Chinese [1–3]. Surgical resection has been accepted as the therapeutic option for patients with resectable esophageal carcinoma in the past 50 years. However, surgical results were dismal except for those with early cancer [4]. Unfortunately, most of patients with esophageal carcinoma are diagnosed at an advanced stage. The role of surgery in treating cancer is limited to cases in which the disease localized at the site of origin, and occasionally in patients with early lymphatic spread in the region. Thus, for patients with advanced cancer, the main aim of surgery, theoretically, is to relieve clinical symptoms, or to prevent tumor-inducing complications, and generally, there is only a little or no improvement in life expectancy.

According to the UICC TNM classification of esophageal carcinoma in 1987 [5], T4 lesion is defined as tumor involving the adjacent structures, including the paraesophageal soft tissues, pericardium, bronchus, aorta, and other great vessels. Basically, it is possible to perform complete resection for T4 lesion of the paraesophageal soft tissues or pericardium. By contrast, advanced T4 esophageal carcinoma is considered an unresectable lesion involving the mediastinal vital organs, such as trachea, aorta, or other great vessels. It is thought that the majority of patients with advanced T4 lesion have a very poor prognosis regardless of radical surgery and the use of combined adjuvant therapy [1,2,4,6]. However, some innovative approaches have been investigated to improve upon the dismal prognosis provided by the current treatment for patients with esophageal carcinoma. Investigations looking for a possible synergism of concurrent radiation and chemotherapy have been reported in recent years and improvements in survival are encouraging [7–13]. Nevertheless, little information has been collected about the treatment of patients with advanced T4 lesions, particularly where comparisons are made between various conservative and aggressive therapeutic modalities at the same time. In this study, various therapeutic modalities for patients with advanced T4 esophageal carcinoma are evaluated to determine the effect of aggressive treatment, thus broadening the scope of therapy.

MATERIALS AND METHODS

From June 1987 to July 1992, a total of 59 consecutive patients with advanced T4 esophageal carcinoma were admitted to the Division of Thoracic Surgery at Veterans General Hospital-Taipei. Among these 59 patients, 17 (28.8%) were found to have evidence of distant metastasis (M1 lesion) or tracheo-esophageal (TE) fistula at admission and were excluded from the study. Thus, only 42 patients who had Karnofsky Performance Scale greater than 70% were entered in the study. The average age of these 42 patients was 65.3 ± 7.8 years. Only one (2.4%) patient was female, the other 41 (97.6%) were men.

After admission, a series of examinations for tumor staging were carried out routinely. They included blood cell counts, biochemistry studies, esophagoscopy with biopsies, bronchoscopy, chest radiography, esophagography, computed tomography (CT) of neck, chest, and upper abdomen, and radionuclide scanning of whole body bone and brain. Pulmonary and cardiac functions were also studied. Epidermoid carcinoma of esophagus was confirmed by histologic examination, and advanced T4 lesion was defined by evidence of tumor invasion into the trachea, bronchus, or aorta for bronchoscopy, CT scan, and operative findings. If the CT scan of the chest showed at least 90° or greater contact, with obliteration of the fat plane between the esophagus and aorta, direct tumor invasion of the aortic wall was assumed [14–16], and magnetic resonance imaging (MRI) would be performed for further confirmation. Patients with obvious endotracheal or endobronchial lesions, or TE fistula, or direct tumor invasion of the whole layers of aortic wall, or evidence of distsant metastasis (M1 lesion) were excluded.

Five therapeutic modes were used in treating these 42 patients (Table I). These five modes were: Group I, no treatment, 6 patients; The patients only underwent feeding jejunostomy (n = 5) or endo-esophageal intubation (n = 1) for nutritional support; Group II, palliative subtotal esophagectomy with incomplete tumor resection, and immediate reconstructive surgery by using the stomach, but no perioperative adjuvant therapy, 8 patients; Group III, bypass procedures to relieve symptom of dysphagia, without tumor resection, 9 patients (5 of these 9 patients received postoperative radiotherapy, two refused the postoperative adjuvant therapy after bypass surgery, and another two died of operative complications); Group IV, conservative treatment with nutritional support (feeding jejunostomy or total parenteral nutrition), then treatment with irradiation (n = 8) or concurrent radio-chemotherapy (n = 4), 12 patients; Group V, subtotal esophagec-

TABLE I. Groups of Various Therapeutic Modes in 42 Patients With Advanced T4 Epidermoid Carcinomas of the Esophagus

Group	No. of patients	Management
I	6	No treatment, except for conservatively nutritional support
II	8	Palliative esophagectomy with residual tumor, plus reconstructive surgery, but no adjuvant therapy
III	9	Bypass procedures without tumor resection; postoperative irradiation for 5 patients
IV	12	Radiotherapy (n = 8), or concurrent chemoradiotherapy (n = 4)
V	7	Subtotal esophagectomy with debulking of tumor and reconstructive surgery with stomach, plus postoperative concurrent chemoradiotherapy

tomy with debulking of tumor and using the stomach as the esophageal substitute, followed by aggressive concurrent chemoradiotherapy, 7 patients.

The assignment to a therapeutic modality was decided by patient choice. When the patient entered the study after a series of pretreatment evaluation, five therapeutic modalities were open for selection by the patient. All patients and their families had the management protocol clearly explained, and they fully understood the possible complications of management and the uncertainties of each therapy.

Intravenous nutritional support had been instituted for more than 10 days before the respective treatments were performed. For the patients undergoing surgical resection of tumor, lymph node sampling for tumor staging was performed, instead of radical extirpation. Residual tumor due to incomplete resection was confirmed by microscopic examination of operative frozen section. In general, postoperative adjuvant therapy was commenced within 1 month if the patient's condition was suitable.

Irradiation was usually directed to the lower neck and the mediastinum. The total prescribed dose of irradiation was 60 Gy (10 Gy/5 fractions/week). The initial irradiation of 40 Gy was administered through anteroposterior (AP)–posteroanterior (PA) portals; then, the final dose of 20 Gy was given through bilateral portals. Concurrent chemotherapy was dispensed for two cycles, at the first and the sixth weeks of irradiation. A combination regimen of chemotherapy consisting of cisplatin (DDP), 20 mg/m^2/day, 5-fluorouracil (5-FU), 600 mg/m^2/day, and leucovorin 120 mg/m^2/day, was administered via 24-hr infusion during a 4-day period in a volume of 2,000 ml normal saline per day. Anti-emetic medication included a combination of metoclopromide, prochlorperazine, and hydrocortisone, or with ondansetron (Zofran) and dexamethasone. For the prevention of nephrotoxicity induced by DDP, patients were hydrated by increasing intravenous fluids with 2,000 ml of 0.45% normal saline and 5% dextrose administered every morning. A small dose of furosemide (20 mg iv, bid) was required to maintain urine output at a rate of more than 100 ml/hr. Complete blood, differential, and platelet counts, serum creatinine, blood urea nitrogen (BUN), SGOT, SGPT, bilirubin, alkaline phosphate, and calcium were monitored during each cycle of chemotherapy or radiotherapy. After completing the treatment, patients were followed up regularly at the outpatient clinic. Barium swallow, esophagoscopy, bronchoscopy, blood tests, abdominal sonogram, chest roentgenography or CT scanning, and radionuclide scanning of whole body bone were repeated for tumor re-staging and evaluating the therapeutic response every 3–6 months.

The results were presented as a mean, plus or minus the standard error of mean (SEM). Statistical analysis of the Chi-square with Fisher's exact test was applied for comparison among groups. For evaluating the differences between the therapeutic results of various group patients, the cumulative proportions of surviving patients, based on the Kaplan–Meier method, were compared using Gehan generalized Wilcoxon test. Statistical significance was assumed for a P-value of <0.05.

RESULTS

The results of the initial evaluation for patients in the five groups are shown in Table II. In comparing these 5 Groups, no statistical difference was observed in terms of age, serum albumin, SGOT, SGPT, serum alkaline phosphatase, blood urea nitrogen (BUN), and creatinine. Significant difference was found in the forced expiratory volume of the first second (FEV1) between Groups II and IV (2.26 ± 1.03L., vs. 1.21 ± 0.92L., $P = 0.037$).

The distribution of tumor location for these 42 patients was 12 (28.6%) for the upper one-third (Tu) of esophagus, 25 (59.5%) for the middle one-third (Tm), and 5 (11.9%) for the lower one-third (Tl). The involved organs consisted of trachea or main bronchus, 36 (85.7%) patients and descending aorta, 6 (14.3%) patients (Table III). Most tumors at the Tu and Tm esophagus invaded the trachea or main bronchus, while those at the Tl esophagus frequently involved the descending aorta.

For patients undergoing esophagectomy or bypass procedures (Groups II, III, V, n = 24), the rates of operative complication and mortality were 45.8% and 25%, respectively (Table IV). The most frequent complications were anastomotic leakage (9 patients, 37.5%) and pneumonia (6 patients, 25%). The causes of surgical mortality included 5 pneumonias with adult respiratory distress syndrome (ARDS) (20.8%, 3 Group II patients and 2 Group III patients) and one acute myocardiac infarction (AMI) (4.2%, one Group II patient). The side effects of adjuvant therapy (n = 24) included trachitis and bronchitis (24 patients, 100%), mucositis or gastrointestinal (GI) symptoms (20 patients, 83.3%), hematological toxicity (19

TABLE II. Clinical Evaluation in Patients With Advanced T4 Epidermoid Carcinomas of the Esophagus, Groups I–V

	Gr I (n = 6)	Gr II (n = 8)	Gr III (n = 9)	Gr IV (n = 12)	Gr V (n = 7)	*P*
Age (yr)	65.2 ± 1.8	65.5 ± 7.7	66.7 ± 8.4	67.0 ± 9.4	60.6 ± 6.9	NS[b]
Hemoglobin (mg%)	11.8 ± 0.6	12.1 ± 2.8	12.7 ± 1.8	12.5 ± 1.6	13.8 ± 1.3	NS
Albumin (g/dl)	3.7 ± 0.6	4.0 ± 0.3	3.7 ± 0.5	3.7 ± 0.6	3.9 ± 0.3	NS
SGOT (M/dl)	21.5 ± 11.1	12.1 ± 8.2	23.0 ± 22.2	17.7 ± 9.8	17.9 ± 7.9	NS
SGPT (U/dl)	28.5 ± 15.9	23.7 ± 14.7	25.9 ± 18.9	24.6 ± 11.4	24.3 ± 6.9	NS
Creatinine (mg/dl)	0.85 ± 0.45	0.78 ± 0.32	0.64 ± 0.39	0.79 ± 0.26	0.84 ± 0.13	NS
FEV1(L)[a]	1.45 ± 1.0	2.26 ± 1.03	1.76 ± 1.14	1.21 ± 0.92	2.08 ± 0.45	0.037[c]

Results were presented with mean ± SEM.
[a]FEV_1, forced expiratory volume of the first second (L)
[b]NS, not significant.
[c]FEV_1, Group I vs. Group II, $P = 0.037$.

TABLE III. Distribution of Tumor Location and Organs of Tumor Invasion for Patients With Advanced T4 Epidermoid Carcinomas of the Esophagus, Groups I–V

Tumor location	Organs of invasion: Trachea and bronchus	Organs of invasion: Aorta	No. of patients (%)
Upper 1/3	12	0	12 (28.6)
Middle 1/3	23	2	25 (59.5)
Lower 1/3	1	4	5
Total:	36 (85.7%)	6 (14.3%)	42 (100)

TABLE IV. Operative Complications and Mortality for Patients With Advanced T4 Epidermoid Carcinomas of the Esophagus, Groups II, III, and V

Complications	No. of patients (%)	Mortality (%)
Anastomotic leakage	9 (37.5)	—
Wound infection	1 (4.2)	—
Pneumonia	6 (25.0)	5 (16.7)[a]
Hoarseness	2 (8.3)	—
AMI[b]	1 (4.2)	1 (4.2)
Total:	11 (45.8)	6 (25.0)

[a]Including three Group II patients and two Group III patients.
[b]AMI, acute myocardial infarction, in one Group II patient.

TABLE V. Side Effects of Adjuvant Therapy of Patients With Advanced T4 Epidermoid Carcinomas of the Esophagus, Groups I–V

Side effects (%)	No. of patients (%)	Mortality (%)
Trachitis/bronchitis	24 (100)	—
Mucositis/GI symptoms[a]	20 (83.3)	—
Hematological toxicity	19 (79.2)	—
Esophagitis or gastric ulcer	15 (62.5)	1 (4.2)
Alopecia	9 (37.5)	—
Pneumonia	5 (20.8)	3 (12.5)[b]
Total:	24 (100)	4 (16.7)

[a]Gastrointestinal (GI) symptoms included anorexia, nausea, and emesis.
[b]Death due to tracheoesophageal fistula formation with pneumonia.

patients, 79.2%), esophagitis or gastric ulcer with odynophagia and dysphagia (15 patients, 62.5%), alopecia (9 patients, 37.5%), and pneumonia (5 patients, 20.8%) (Table V). Four patients died during adjuvant therapy. It involved two Group IV patients (TE fistula formation and pneumonia), and two Group V patients (one gasric ulcer with massive bleeding and another one TE fistula with pneumonia). Thus, the rate of mortality due to toxic effects of adjuvant therapy was 16.7% (4/24 patients).

Among these 42 patients, 3 Group V patients are surviving at the time of writing (Table VI). The mean survival times of these 5 groups were 1.9 ± 0.5 months for Group I, 4.8 ± 1.6 months for Group II, 5.2 ± 1.2 months for Group III, 7.3 ± 2.0 months for Group IV, and 20.3 ± 2.5 months for Group V, respectively. The overall mean survival time of these 42 patients was 7.3 ± 1.0 months. Except for 10 patients who died of operative complications (n = 6) and the side effects of adjuvant therapy (n = 4), all other patients (n = 29) died from carcinomatosis. The cumulative survival curves for these 5 groups were shown in Figure 1. The 1-year survival rates was 0% for Groups I and II, 11.1% for Group III, 16.7% for Group IV, and 71% for Group V, respectively. There was no difference between survival curves for Groups II to IV patients, but the Group V patients had a significantly better survival curve than patients in the other 4 groups ($P < 0.01$), while Group I patients had the worst prognosis compared to patients of Groups II–V ($P < 0.05$).

Three Group V patients (n = 7) are still alive (currently 24, 28, and 38 months, respectively) after surgical resection, and no evidence of tumor recurrence was detected in the follow-up study. These three patients have tolerated a second or third course of PFL regimen chemotherapy 3–4 months after the initial esophagectomy and concurrent radiochemotherapy. In Group IV patients being treated with irradiation (n = 8) or concurrent combination radiochemotherapy (n = 4), eight (75%) obtained an im-

TABLE VI. Survival Status and Causes of Death in Patients With Advanced T4 Epidermoid Carcinomas of the Esophagus, Groups I–V

Groups	No. of patients	Mortality (%)	Mean survival time (±SEM) (mo)	Carcinomatosis	Complications	
					Surgery	Chemo-radiotherapy
I	6	6 (100)	1.9 ± 0.5	6		
II	8	8 (100)	4.8 ± 1.6	4	4	
III	9	9 (100)	5.2 ± 1.2	7	2	
IV	12	12 (100)	7.3 ± 2.0	10		2
V	7	4 (57.1)	20.3 ± 2.5	2		2
Total:	42	38 (90.5)	7.7 ± 1.0	29 (69.1%)	6 (14.3%)	4 (9.5%)

SEM, standard error of means.

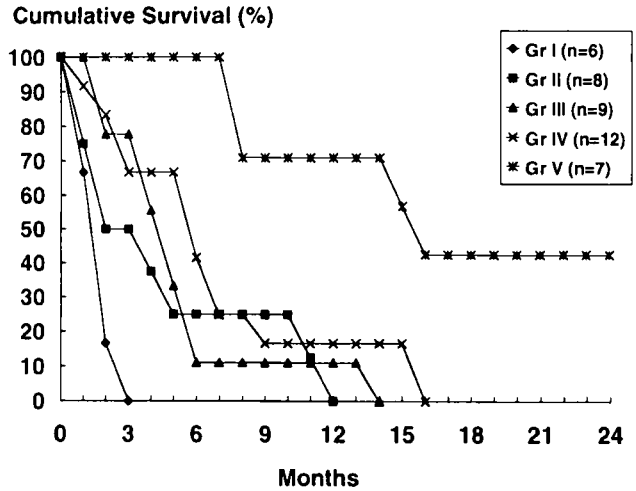

Fig. 1. Cumulative survival curves for five groups of the patients with advanced T4 esophageal carcinoma, based on the Kaplan–Meier method, were shown. Using Gehan generalized Wilcoxon test, no statistical difference in survival curves was found among patients of Groups II, III, and IV, while Group V patients had a signficantly superior survival rates ($P < 0.01$). Group I patients had the worst in survival prognosis ($P < 0.05$), compared with the other four groups.

provement in the ability to swallow (4 patients with irradiation, and 4 patients with concurrent combination radiochemotherapy). However, all Group IV patients had residual tumor in esophagoscopic biopsy after adjuvant therapy. Thus, for the Group IV patients, partial response rate was 75%, but no complete response was achieved. Patients undergoing bypass, or reconstructive surgery of the esophagus (Groups II, III, and V) generally gained an improved ability to swallow compared to those without esophageal substitution (Groups I and IV).

DISCUSSION

Results in treatment of esophageal carcinoma have been far from satisfactory, particularly for late-stage lesions. Once the diagnosis of late staged carcinoma of the esophagus is made, there is little agreement on the best therapeutic approach to take with patients. In the management of patients with advanced T4 esophageal carcinoma, the main goal is to restore the patient's nutrition, or swallowing ability, and to improve their quality and quantity of life.

Although preoperative adjuvant therapy might have been associated with modest response rates [10–13,17], several investigators [11,18–22] and previous experience have shown that neoadjuvant therapy could produce a rather severe dysphagia, delayed esophageal stricture or fistula, pericaditis, tracheobronchial irritation, or myelitis. These toxic effecs can undermine the originally poor condition of the patients with advanced cancers, and may hinder the performance of esophagectomy. Leichman and colleagues [11,17] described a promising regimen consisting of preoperative chemotherapy with 5-fluorouracil (5-FU) and cisplatin and concurrent radiotherapy, followed by esophagectomy. However, their operative mortality was unacceptably high. Even in this study, without preoperative adjuvant therapy, undergoing a major operation for patients with advanced T4 carcinoma of the esophagus causes relatively high morbidity and mortality rates (45.8% and 25%, respectively). Hilgenberg and associates [12] have pointed out that problems with multiple programs for the treatment of esophageal carcinoma include (1) toxicity from the preoperative regimen; (2) poor condition of patients when they undergo resection; (3) delay between diagnosis and resection; (4) operative mortality; and (5) local and systemic recurrence of cancer, or both. Furthermore, it has been concluded that survival and potential cure only be predicted for the patients who have no cancer in the resected esophageal specimens through properative treatment, and all those with residual cancer in the esophagus and lymph node were still linked to poor prognosis [11,12]. In our series, all Group IV patients had residual cancer in the esophagoscopic biopsies, and it was believed that these patients with advanced T4 tumor could not tolerate further esophagectomy because of their poor condition after radiochemotherapy. Thus, preoperative adjuvant therapy was not established for patients with advanced T4 carcinoma of the esophagus.

Many reports have demonstrated that esophageal carcinoma is relatively sensitive to irradiation and chemotherapy. Moreover, the proper choice of chemotherapy regimen can make a great difference in improving the response rate [11]. A combination regimen of cisplatin and 5-FU (PF regimen) has been suggested to be the most effective adjuvant therapy for patients with esophageal carcinoma. Both these chemotherapeutic agents are synergistic [23,24] and have the properties of radiation sensitizers [25,26]. In the present study, a moderate dose of leucovorin was added to PF combination chemotherapy. The combination regimen of PFL has shown significant activity in patients with squamous cell carcinoma of the head and neck [23,27–29]. A clinical response of PFL regimens was achieved in more than 80% of patients with advanced carcinoma of the head and neck. It has also been shown that higher complete response rates can be achieved with more cycles of PFL chemotherapy when treating squamous cell carcinoma of the head and neck [23,30,31].

Leucovorin, or folinic acid, has been used as a biochemical modulator that alters potential pathways of tumor resistance or 5-FU degradation, and may improve the therapeutic efficacy of 5-FU [32–35]. A major mechanism by which 5-FU exerts cytotoxic effects is the inhibition of thymidylate synthetase, a critical enzyme in metabolic reactions leading to the synthesis of DNA. Inhibition of thymidylate synthetase by 5-FU can be enhanced by an increase in the intracellular folate levels. Although several investigators have suggested using higher doses of leucovorin (150–600 mg/m^2/day) for potentiation of 5-FU cytotoxicity [27,28,30], Poon and coworkers [31] have demonstrated in a randomized study that there was no significant survival difference between 5-FU plus high-dose leucovorin (200 mg/m^2/day) and 5-FU plus low-dose leucovorin (20 mg/m^2/day) in treating patients with advanced colorectal carcinoma. One mmol/L serum levels of leucovorin can be achieved by the administration of a dose in the range of 10–20 mg/m^2 in human [36]. In this study, a moderate dose of leucovorin (120 mg/m^2/day) was chosen in a PFL combination chemotherapy. All patients receiving PFL combination chemoradiotherapy had developed rather severe toxic effects, particularly mucositis, hematogenic toxicity, and main airway irritation. We use a rather low daily dose of DDP (20 mg/m^2/day) by 24-hr infusion for a 4-day period, because this is a rather sick group of patients and toxic effects of the adjuvant therapy is high.

It has been emphasized that if the stomach is brought up to replace the esophagus, the irradiation dose must be limited to 45–50Gy because of the gastric radiation sensitivity [37]. In this study, esophageal substitution was performed by gastric transplant through the retrosternal route [3]. The postoperative irradiation was administered with an initial 40 Gy through AP-PA portals, and then the final dose of 20 Gy through bilateral portals, to increase the irradiation dose to the posterior mediastinum, but to diminish the side effects of gastritis or gastric ulcer. Nevertheless, the post-irradiation gastritis, or gastric ulcer, occurred in a rather high incidence (62.5%) in our patients. One patient died of massive bleeding due to an irradiation gastric ulcer. Generally, proper management can ensure complete recovery from these toxic side effects of adjuvant therapy within 2–3 weeks.

Hilgenberg et al. [12] and Orringer et al. [38] have strongly recommended that resection of the esophagus should not be omitted in the treatment plan of the patient undergoing adjuvant therapy for locoregional disease. For patients with advanced T4 lesion, it is extremely difficult to obtain a better improvement in survival either through a simple palliative esophagectomy, or aggressive chemoradiotherapy, although these treatments appear to offer survival advantage over supportive care. The results disclosed that esophagectomy with tumor debulking, followed by an aggressive concurrent chemoradiotherapy as soon as possible, provide a chance of intermediate survival, in addition to improving the quality of life. The improvement in survival was particularly obvious in those who could tolerate two or more cycles of a PFL combination chemotherapy. However, a proper selection of patients and good peri-operative management are essential in carrying out this aggressive multi-modality therapy. We suggest that an aggressive multimodality therapy had better not be carried out for the patients with the following conditions: (1) evidence of distant metastasis or an obvious endotracheal, or endobronchial, tumor, or a whole layers invasion of the aorta; (2) old age (>75 years); (3) moderate to severe malnutrition (serum albumin <3.5 g%); (4) poor pulmonary function (FEV_1 <1.5 L, total vital capacity <2.5 L); (5) long history of excessive cigarette smoking and alcohol use; (6) an association with several systemic diseases, e.g., recent myocardial infarction or cerebral vascular accidents (within 6 months), uncontrollable diabetes or hypertension, severe chronic obstructive pulmonary disease, etc. For perioperative management, the utmost care was taken with the patient's nutritional status and prevention of pulmonary complications. Operative complications, particularly anastomotic leakage (37.5%) and pneumonia (25%), were quite high (45.8%) for our patients undergoing esophagectomy and bypass procedures, despite the fact that preoperative nutritional support had been routinely established for more than 10 days. Except for intravenous nutritional support, jejunostomy tube was kept for feeding throughout the course of postoperative adjuvant therapy, due to a high incidence of mucositis, esophagitis or gastritis, and other gastrointestinal side effects which may develop and discourage the patient's oral intake of food.

There was concern that a TE fistula could be left after chemotherapy or irradiation therapy has destroyed the

tumor that subclinically eroded into the main airway. Lewinsky and associates [37] have described an incidence of 10.6% developing TE fistula after irradiation treatment for 85 patients with esophageal carcinoma. Nevertheless, in an analysis of 41 patients with malignant TE fistula arising as a result of esophageal cancer at the Mayo Clinic, Gschossmann et al. [39] did not observe any cases of TE fistula formation due to lysis of a tumor that had transverse through the esophageal wall and into the trachea. It has been further recommended that radiation therapy does not appear to increase the severity of the TE fistula [39,40]. In the present study, we found three patients (15.6%) developing TE fistula who died of ARDS during the period of chemoradiotherapy. We believe that tumor involving the submucosal layer of trachea, or the partial aortic wall invasion, can be treated by chemoradiotherapy with a rather low risk of fistula formation.

We admit that patient selection in a nonrandomized fashion and the small numbers in each group may affect the statistical accuracy of the result in this study. However, the present result is encouraging, and may provide an additional support for multimodality treatment in patients with esophageal carcinoma. Additionally, patients receiving the rconstructive surgery after esophagectomy could have a better quality of life, in particular, having the ability to enjoy oral intake of food, instead of tube feeding. The result observed with pre- or postoperative concurrent irradiation and PFL therapy require further confirmation, and the impact of this multimodality therapy on local tumor control and survival prognosis remains to be determined in other stage II and III patients in a randomized study.

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COMMENTARY

Wang and colleagues have reported their experience with 42 patients with T4 epidermoid carcinoma of the esophagus treated in a five year interval. Patients were divided into Group I, who received no specific anti-tumor therapy plus or minus a feeding jejunostomy or intubation. Group II, received subtotal esophagectomy with incomplete tumor resection, and no perioperative adjuvant therapy. Group III, received a bypass procedure without tumor resection and some had postoperative radiotherapy. Group IV, received nutritional support and radiation or concurrent chemo-radiation. Group V received a subtotal debulking esophagectomy followed by aggressive concurrent chemoradiotherapy. Although the authors report no significant differences in various parameters among the groups, it is difficult to disprove the existence of a selection bias in which four groups of patients receive some treatment and one (Group I) received no anti-tumor therapy and treatment. Esophagectomy or bypass procedures among these patients was accompanied by a 25% mortality and a 45.8% complication rate. The mortality related to toxicity of adjuvant therapy was over 20%. The only group with a statistically significant improvement in survival compared to the other four groups was Group V. The material and methods section does not mention how or if Group V patients had reestablishment of gastrointestinal tract continuity but the results section indicates that some did receive bypass or reconstructive surgery.

The results of aggressive treatment administered to the Group V patients is statistically significant compared to those treated in other ways and, of course, better than those who received no anti-tumor treatment (Group I patients). It has been previously pointed out that statistically significant differences in small studies with unclear criteria for inclusion (or exclusion) in the superior treatment group vs. others may be explained by selection bias rather than by a truly superior treatment [1]. We look forward to future studies of Dr. Wang and colleagues comparing Group V patients with a single control group treated in a cost efficient fashion. It is noteworthy that the survival of patients in Groups I through IV is no better than that provided by a single treatment of high dose rate radiation [2]. This treatment administered 1,250 cGy in one fraction to a depth of 1 cm. This dose is delivered by a remote afterloader using an Iridium-192 source. Total treatment is accomplished in less than one half an hour in one day compared with weeks of treatment required for the authors' Groups II through IV.

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